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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/542,759

08/16/2005

Gary Mark Coppola

4-32859A

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05/22/2009

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
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CAMBRIDGE, MA 02139

EXAMINER

MABRY, JOHN

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

05/22/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/542,759	Applicant(s) COPPOLA ET AL.	
	Examiner JOHN MABRY	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-9, 12, 13, 18-20, 22 and 25-33 is/are pending in the application.
- 4a) Of the above claim(s) 25-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-9, 12-13, 18-20, 22 and 33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on March 4, 2009 has been entered.

Restriction Requirement

For matters of convenience, Examiner reminds Applicant of the elected Group I **without traverse** dated March 6, 2008. This election was made final in Non-Final Office Action dated April 8, 2008. Considerable prosecution and claim amendments has since taken forth; however, Examiner has noticed that Applicant still has not conformed to portions of the election as seen in the most current set of claims.

- I. Claims 1, 2, 3, 7, 8, 9, 11, 12, 13, 18, 19, 20, 22, 33 and 37 are drawn to compounds and pharmaceutical compositions of Formulas Ia, Ih and li, wherein X,Y=C (phenyl and naphthyl – no additional ring fusing) R₃ and R₄ forms hydroquinoline. A further election of single disclosed species is required.

Interview Summary

Examiner acknowledges telephonic interview along with Primary Examiner Rita Desai with Attorney Mark Milstead on April 6, 2009.

Response to Amendment(s)

Applicant's response on January 21, 2009 filed in response to the Office Action dated November 4, 2008 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

Status of the Claims

Claims 7-9, 12-13, 18-20, 22 and 33 are pending and rejected.

Claims 1-6, 10-11, 14-17, 21, 23-24 and 34-39 have been cancelled.

Claims 25-32 directed towards non-elected subject matter.

35 USC § 112 Rejection(s)

Rejection of claims 7-9, 12-13, 18-20, 22 and 33 are maintained under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R1 and R2=H, amino, alkyl amino, nitro, halo, CF3, CO2H, CO2alkyl, CONHalkyl, alkoxy, alkyl unsubstituted and substituted with phenyl, cyano and R6-R9=unsubstituted phenyl, naphthyl, thienyl, furanyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, pyridinyl, benzothiophenyl, benzodioxolyl and cycloalkyl and substituted with halogen, alkoxy, NH2, NO2, cyano, does not reasonably provide enablement for all heterocyclic, aryl and heteroaryl groups as claimed. Additionally, the hydroquinoline and isohydroquinoline are only enabled as being unsubstituted and R13/R14 being methyl and OH. The term

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“optionally substituted” is not fully enabled as well. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to making the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Specification does not provide any support for said variables at R1, R2 and R6-R9 positions. Pages 50-81 of the Specification describe starting materials and methods for synthesis of compounds wherein R1 and R2=H, amino, alkyl amino, nitro, halo, CF₃, CO₂H, CO₂alkyl, CONHalkyl, alkoxy, alkyl unsubstituted and substituted with phenyl, cyano and R6-R9=unsubstituted phenyl, naphthyl, thienyl, furanyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, pyridinyl, benzothiophenyl, benzodioxolyl and cycloalkyl and substituted with halogen, alkoxy, NH₂, NO₂, cyano, but does not describe or list any reagents wherein compounds can be used to synthesis compounds of said variables as listed above.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention

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based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted quinoline and isoquinoline amide compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted quinoline and isoquinoline amide compounds.

(3) Level of predictability in the art: It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application’s general formula I. Pages 50-81 of the Specification describes starting materials and methods for synthesis of compounds wherein R1 and R2=H, amino, alkyl amino, nitro, halo, CF3, CO2H, CO2alkyl,

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CONHalkyl, alkoxy, alkyl unsubstituted and substituted with phenyl, cyano and R6-
 R9=unsubstituted phenyl, naphthyl, thienyl, furanyl, pyrrolyl, morpholinyl, piperidinyl,
 piperazinyl, pyridinyl, benzothiophenyl, benzodioxolyl and cycloalkyl and substituted
 with halogen, alkoxy, NH₂, NO₂, cyano, but does not describe or list any reagents
 wherein compounds can be used to synthesis compounds for all heterocyclic, aryl and
 heteroaryl groups as claimed in R1, R2 and R6-R9 as listed above. There is limited
 evidence in the Specification of the example compounds that only covers no or a small
 portion of the substituents claimed of formula. Thus, there is no specific direction or
 guidance regarding said compounds specifically mentioned in Scope.

For instance, Applicant has claimed compounds of Formula Ia where:

W is -NR₅C(O)R₆, -NR₅C(O)OR₆, -NR₅C(O)NR₆R₇, -NR₅C(S)NR₆R₇, -NR₅S(O)₂R₆,
 -NR₅R₆, -C(O)NR₆R₇ or -OC(O)NR₆R₇ in which

R₅ and R₇ are independently hydrogen or methyl; or

R₅ and R₇ are alkylene which combined together with the nitrogen atom to which
 R₅ is attached and the carbon atoms to which W and R₇ are attached form a 5-membered ring;

R₆ is optionally substituted alkyl, aryl, heteroaryl heteroaryl, cycloalkyl, aralkyl or
 heteroaralkyl, wherein said aryl is optionally substituted by one to four substituents such as halo,
hydroxy, alkoxy, alkanoyl, alkanoyloxy, optionally substituted amino, thiol, alkylthio, nitro, cyano,
carboxy, carboxyalkyl, alkoxycarbonyl, alkylthiono, alkyl- and arylsulfonyl, sulfonamido and
heterocycloyl;

R₆ is optionally substituted alkyl, aralkyl or heteroaralkyl;

R₆ is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl or alkanoyl; or

-or-

Applicant has only provided guidance for W being -NR₅C(O)R₆ where R₅ is H
 and R₆ is phenyl with several simple optional substituents as shown in Examples 9, 10

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and 11 on pages 48-50). This specified section only gives guidance for "Title Compound B" - essentially a substituted amine (-NH₂) reacting with "benzoyl chlorides" to form compounds of Formula Ia. Applicant has confirmed this fact in Remarks to Final Office Action date January 21, 2009 (see bottom of page 10 and top of page 11). As aforementioned, R₈ is enabled for unsubstituted phenyl, naphthyl, thienyl, furanyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, pyridinyl, benzothiophenyl, benzodioxolyl and cycloalkyl and substituted with halogen, alkoxy, NH₂, NO₂, cyano, but does **not** describe or list any reagents wherein compounds can be used to synthesis compounds of said variables as listed above, especially for the entire term "heteroaryl" and "optionally substituted" variables as claimed. Applicant has not provided guidance for W being functional group other than "-NR₅C(O)R₆" and aryl and heteroaryl groups of R₆ being the entire claimed scope as claimed - aryl and heteroaryl as defined on pages 5 and 7, respectively of Specification.

A search of acid halides in the Sigma-Aldrich Catalog has provided some starting materials in order synthesized claimed compounds of Formula Ia (see attached catalog provided). Sigma-Aldrich Catalog provides starting materials for some of the final products that Applicant has shown, but does not provide guidance for the entire scope as claimed. Additionally, it is not certain that all starting materials are chemically compatible with guidance Applicant has provided in the Specification. It would that a skilled artisan of ordinary skill to attempt to synthesize these products with available starting materials in order to see if reagents are compatible with guidance provided to make compounds of claimed Formula Ia. Additionally, there is no guidance to

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synthesize acid halide starting materials that are not commercially available. This would certainly provide an undue experimental burden.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here...As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In *re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

(5) State of the Prior Art: These compounds are substituted quinoline and isoquinoline amide compounds wherein R1, R2 and R6-R9 which are well documented in the art. So far as the examiner is aware, no substituted quinoline and isoquinoline amide compounds of general formula I wherein R1, R2 and R6-R9 equals all heterocyclic, aryl and heteroaryl groups as claimed of any kind have been made or used.

It is not trivial to experimentally interchange any and all of the many substituents that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(6) Working Examples: Applicant shows examples in table on pages 50-81 but no working examples were shown wherein R1, R2 and R6-R9 equal aforementioned substituents and ring systems have been made or used of any kind.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

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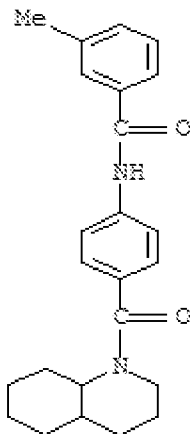
Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has shown lack of enablement for the groups noted.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 102

Claims 7, 8 and 33 rejections are maintained under 35 U.S.C. 102(b) as being anticipated by Ogawa et al (WO 9401113 A1).

Ogawa et al clearly discloses compounds and pharmaceutical compositions of Formulas Ia wherein R13 and R14=H, X and Y=CH, R1 and R2=H and W=NR5C(O)R6 wherein R5=H and R6=methylphenyl (see compound 2-149, page 146).



Claim Rejections - 35 USC § 103

Claims 18, 19, 20 and 33 rejections are withdrawn under 35 U.S.C. 103(a) as being unpatentable over Matsumoto et al (WO 2003029199 - US equivalent 2004/0259912 A1) in view of reconsideration by Examiner.

An action on the merits of the claims is contained herein below.

DETAILED ACTION

Claim Objections

Claims 18, 19, 20 and 22 are objected to as being dependent upon cancelled claim 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

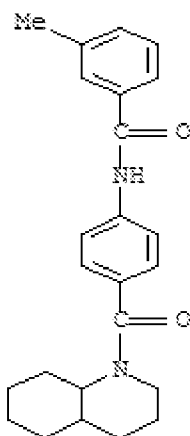
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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 7, 8, 9 and 33 rejected under 35 U.S.C. 103(a) as being unpatentable over Ogawa et al (WO 9401113 A1).

Scope & Content of Prior Art MPEP 2141.01

Ogawa et al discloses compounds and pharmaceutical compositions of Formulas Ia wherein R13 and R14=H, X and Y=CH, R1 and R2=H and W=NR5C(O)R6 wherein R5=H and R6=methylphenyl (see compound 2-149, page 146).



Differences between Prior Art & the Claims MPEP 2141.02

Ogawa and the instant application differs at the R1 position: Ogawa's H versus Applicant's CH3. A hydrogen (H) and methyl (-CH3) are deemed obvious variants (*In re Wood*, 199 USPQ 137).

Furthermore, the genus of Formula 2, page 11 of the reference by Ogawa teaches R17 =H, halogen, lower alkoxy, and lower alkyl and substituted amino (see page 11, definition of R17). These teachings of Ogawa are the same that are being claimed by Applicant. Thus said, claims are rendered obvious Ogawa.

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be “obvious” for one of ordinary skill “to try” to make compounds of Formula Ia choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success from the disclosed compounds and teachings of Ogawa. In further view of Ogawa’s species, teachings and suggestions would lead one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” KSR, 550 U.S. at ___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield

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- predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. v. Teleflex Inc. decision. Letters (A) - (E) rationale is supported above.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/

Primary Examiner, Art Unit 1625